TRANSMITTAL LETTTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

Attorney Docket No. 00060

U.S. Application No (if known, see 37 CFR 1.5)

09/508670

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR98/02098	October 1, 1998	October 1, 1997

TITLE OF INVENTION

USE OF ELLAGIC ACID AND ITS DERIVATIVES IN COSMETICS AND DERMATOLOGY

APPLICANT(S) FOR DO/EO/US

Frederic BONTE and Alex SAUNOIS

Applicant herewith submits to the United States Designated Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3).
   a. ☐ are transmitted herewith (only if not required by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5).

Items 11 to 16 below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ As assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

17. ☐ The following fees are submitted: **BASIC NATIONAL FEE (37 CFR 1.492 (a)(1)-(5):** Neither international preliminary examination fee (37 CFR 1.482) Nor international search fee (37 CFR 1.445(a)(2) paid to USPTO And International Search Report not prepared by EPO or JPO.....$970.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by EPO or JPO.....$840.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$690.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) But all claims did not satisfy provisions of PCT Article 33(1)-(4).....$670.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) And all claims satisfied provisions of PCT Article 33(1)-(4).....$96.00	**CALCULATIONS** PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$840.00	
Surcharge of **$130.00** for furnishing oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	31 -20=	11	X $18.00	$198.00	
Independent Claims	3 -3=	0	X $78.00	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				$	
TOTAL OF ABOVE CALCULATIONS =				$1038.00	
Reduction of ½ for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$1038.00	
Processing fee of **$130.00** for furnishing English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f).				$	
TOTAL NATIONAL FEE =				$1038.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31).				$40.00	
TOTAL FEES ENCLOSED =				$1078.00	
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $1078.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 04-0753 in the amount of $ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 04-0753. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
Dennison, Scheiner, Schultz & Wakeman
612 Crystal Square 4
1745 Jefferson Davis Highway
Arlington, VA 22202-3417
Telephone (703) 412-1155 Ext. 23
Facsimile (703) 412-1161

Ira J Schultz

SIGNATURE
Ira J. Schultz

NAME
28666

REGISTRATION NUMBER

Dkt. 00060

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Group Art Unit:

Frederic BONTE et al Examiner:

Serial No: US National Phase of PCT/FR98/02098

Filed: Concurrently herewith

For: USE OF ELLAGIC ACID AND ITS DERIVATIVES IN COSMETICS AND DERMATOLOGY

PRELIMINARY AMENDMENT AND INFORMATION DISCLOSURE STATEMENT

Honorable Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

Before calculation of the filing fee, please amend the application as follows:

IN THE TITLE:

Amend the title to read as follows:

--A METHOD OF COSMETIC CARE USING ELLAGIC ACID, ITS SALTS, METAL COMPLEXES, ETHERS AND ACYLATED DERIVATIVES THEREOF--

IN THE SPECIFICATION:

Page 1, line 4, insert --BACKGROUND OF THE INVENTION--;

line 11, change "20th" to --12th--.

Page 2, between lines 31 and 32, insert --SUMMARY OF THE INVENTION--.

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

Page 3, between lines 14 and 15, insert --DETAILED DESCRIPTION OF THE INVENTION--.

Page 4, line 16, change "metal complex salts" to --salts, its metal complexes--;

line 23, delete "of".

IN THE CLAIMS:

Page 15, line 1, change "CLAIMS" to --WHAT IS CLAIMED IS:--

Please cancel 2 to 16 without prejudice or disclaimer of the subject matter thereof, and add the following new claims:

--17. A method of cosmetic care comprising delivering to skin or hair of a person in need thereof, a cosmetically effective amount of an ellagic component selected from the group consisting of ellagic acid, an ellagic acid salt, an ellagic acid metal complex, an ellagic acid monoether, an ellagic acid polyether, an ellagic acid monoacylated compound, an ellagic acid polyacylated compound, optionally in combination with a cosmetically acceptable excipient.

18. The method of claim 17, wherein said ellagic component is present in a cosmetic composition comprising from 0.001% to 5% by weight of said ellagic component.

19. The method of claim 17, wherein said ellagic component is present in a cosmetic composition comprising from

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

0.01% to 5% by weight of said ellagic component.

20. The method of claim 17, wherein said ellagic component is present in a cosmetic composition comprising from 0.01% to 1% by weight of said ellagic component.

21. The method of claim 17, wherein said ellagic component is present in a cosmetic composition further containing at least one substance selected from the group consisting of a substance which promotes synthesis of at least one extracellular matrix constituent of the of the skin and a substance which regulates the formation of the skin corneal layer.

22. The method of claim 21, wherein said substance is selected from the group consisting of a vitamin, a tocopherol, a xanthine, a retinoid, an extract of Centella asiatica, asiatic acid, madecassic acid, a glycosylated asiatic acid, a glycosylated madecassic acid, an extract of Siegesbecka orientalis, an extract of Commiphora mukul, an extract of Eriobotrya japonica and a mineral compound.

23. The method of claim 22, wherein said vitamin is selected from the group consisting of a vitamin of group A, an ester of a vitamin of group A, a vitamin of group C and an ester of vitamin of group C; said xanthine is caffeine or theophylline; said retinoid is vitamin A acid; said glycosylated asiatic acid is asiaticoside and said

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

glycosylated madecassic acid is madecassoside.

24. The method of claim 21, wherein said mineral compound is selected from the group consisting of a magnesium compound, a manganese compound, a silicon compound and a zinc compound.

25. The method of claim 24, wherein said magnesium compound is selected from the group consisting of magnesium chloride and magnesium aspartate, said manganese compound is manganese chloride, and said silicon compound is a silanol.

26. The method of claim 17, wherein said ellagic acid salt is selected from the group consisting of an ellagic acid alkali metal salt, an ellagic acid alkaline earth metal salt, an ellagic acid amine salt, and an ellagic acid amino acid salt.

27. The method of claim 26, wherein said alkali metal is sodium and said alkaline earth metal is calcium, said amine is selected from the group consisting of methylglutamine, diethanolamine, triethanolamine, choline and bis-triethylamine, and said amino acid is a basic amino acid is arginine, lysine or ornitine.

28. The method of claim 17, wherein said ellagic acid metal complex contains a metal selected from the group consisting of zinc and copper.

29. The method of claim 17, wherein the monoacylated and

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

polyacylated ellagic acid comprises a saturated or unsaturated acyl group having from 2 to 22 carbon atoms.

30. The method of claim 29, wherein said acyl group is an acyl moiety of an acid selected from the group consisting of acetic acid, palmitic acid, oleic acid, linoleic acid, linolenic acid, arachidonic acid, stearic acid, brassidic acid, erucic acid, behenic acid and (all Z)-5,8,11,14,17-eicosapentaenoic acid.

31. The method of claim 17, wherein said ether moiety in the ellagic acid monoether and the ellagic acid polyether is an alkoxy moiety comprising from 1 to 4 carbon atoms.

32. The method of claim 17, wherein said ellagic acid monoether or ellagic acid polyether is a condensation product of at least one ellagic acid hydroxyl group with a sugar.

33. The method of claim 31, wherein said sugar is selected from the group consisting of glucose, arabinose, rhamnose and galactose.

34. The method of claim 17, wherein said ellagic component is selected from the group consisting of 3-methoxyellagic acid, 3-methoxyellagic acid monoether, 3-methoxyellagic acid polyether and a 3-methoxyellagic acid sugar condensation product.

35. The method of claim 17, wherein said ellagic component is present in a composition further comprising at

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

least one substance selected from the group consisting of an aliphatic C_3-C_{12} alpha-hydroxy acid, an amino acid, a ceramide, a glycoceramide, a phospholipid, a slimming agent, an extract of Coleus, an extract of Tephrosia, an agent for combating stretch marks, an agent for protecting or improving microcirculation of blood and a sunscreen.

36. The method of claim 35, wherein said alpha-hydroxy acid is selected from the group consisting of citric acid, malic acid and lactic acid; said amino acid is selected from the group consisting of arginine, citrulline and threonine; said slimming agent is forskolin; said agent for combating stretch marks is an extract of horse-chestnut or escin; said agent for protecting or improving the blood microcirculation is a bioflavonoid of Ginkgo biloba and said sunscreen is selected from the group consisting of a titanium oxide, acyl methoxycinnamate and a sunscreen of a vegetable origin.

37. The method of claim 17, wherein said ellagic component is present in a composition further comprising at least one further active substance selected from the group consisting of an antidandruff agent, an antiseborrhea agent and an agent for stimulating the blood microcirculation.

38. The method of claim 37, wherein said antidandruff agent is selected from the group consisting of an extract of Arctium lappa, chloroxylenol, resorcinol and zinc pyrithione;

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

said antiseborrhea agent is a 5α-reductase inhibitor; and said agent for stimulating the blood microcirculation is cepharanthine or methyl nicotinate.

39. The method of claim 38, wherein said 5α-reductase inhibitor is an extract of Pygeum africanum.

40. The method of claim 17, wherein said cosmetic care method is selected from the group consisting of improving cohesion between dermis and epidermis, toning up skin, slowing down appearance of signs of skin ageing, slowing down appearance of wrinkles or reducing their depth, and improving hair condition.

41. The method of claim 17, wherein said cosmetic care method is for increasing content of collagen VII in the skin.

42. A method of treatment of a patient suffering from a symptom or pathological condition associated with an insufficiency of collagen VII, comprising administering to the person a pharmaceutically effective amount of an ellagic component selected from the group consisting of ellagic acid, an ellagic acid salt, an ellagic acid metal complex, an ellagic acid monoether, an ellagic acid polyether, an ellagic acid monoacylated compound, and an ellagic acid polyacylated compound, optionally in a pharmaceutically acceptable excipient.

43. The method of claim 42, wherein said treatment is

LAW OFFICES
DENNISON, SCHEINER, SCHULTZ & WAKEMAN
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

for treating epidermolysis bullosa.

44. The method of claim 42, comprising administering to the patient from 0.001% to 5% by weight of said ellagic component present in a pharmaceutical composition.

45. The method of claim 42, comprising administering to the patient from 0.01% to 5% by weight of said ellagic component present in a pharmaceutical composition.

46. The method of claim 42, comprising administering to the patient from 0.01% to 1% by weight of said ellagic component present in a pharmaceutical composition.--

AFTER CALCULATION OF THE FILING FEE AND GRANTING OF A FILING DATE, PLEASE CANCEL CLAIM 1 WITHOUT PREJUDICE OR DISCLAIMER OF THE SUBJECT MATTER THEREOF.

REMARKS

Claims 17 to 46 are submitted for initial examination in this application. The new claims have been drafted in accordance with US patent law and practice, notably by canceling use claims 1 to 15 and replacement by method claims.

Submitted herewith is the search report of the corresponding International Application, together with copies of the references cited therein, and listed on the attached

LAW OFFICES
DENNISON, MESEROLE, SCHEINER & SCHULTZ
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

form PTO-1449.

Respectfully submitted,

Ira J. Schultz
Registration No. 28666

LAW OFFICES
DENNISON, MESEROLE, SCHEINER & SCHULTZ
612 CRYSTAL SQUARE 4
1745 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202-3417
703 412-1155

Dkt. 00060

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Group Art Unit:

Frederic BONTE et al Examiner:

Serial No: US National Phase of PCT/FR98/02098

Filed: Concurrently herewith

For: USE OF ELLAGIC ACID AND ITS DERIVATIVES IN COSMETICS AND DERMATOLOGY

PRELIMINARY AMENDMENT AND INFORMATION DISCLOSURE STATEMENT

Honorable Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

Before calculation of the filing fee, please amend the application as follows:

IN THE TITLE:

Amend the title to read as follows:

--A METHOD OF COSMETIC CARE USING ELLAGIC ACID, ITS SALTS, METAL COMPLEXES, ETHERS AND ACYLATED DERIVATIVES THEREOF--

IN THE SPECIFICATION:

Page 1, line 4, insert --BACKGROUND OF THE INVENTION--;

line 11, change "20th" to --12th--.

Page 2, between lines 31 and 32, insert --SUMMARY OF THE INVENTION--.

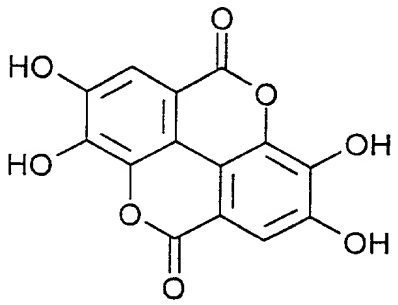
USE OF ELLAGIC ACID AND ITS DERIVATIVES IN COSMETICS AND DERMATOLOGY

The present invention relates essentially to a novel use of ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or polyacylated derivatives in the field of cosmetics or pharmacy, especially dermatology.

Ellagic acid, which also has the name 2,3,7,8-tetrahydroxy(1)-benzopyrano(5,4,3-cde)(1)benzopyran-5,10-dione, is a well-known molecule belonging to the group of the polyphenols and is found in the plant kingdom. Reference may be made to the publication Merck Index 20th edition (1996), no. 3588.

Document FR-A-1 478 523 has disclosed a process for the purification of ellagic acid and the purified ellagic acids obtained by such a process.

Ellagic acid has the following chemical formula:



which contains four fused rings.

Ellagic acid is commercially available in particular from Extra Synthèse, France.

Document EP-A-0 496 173 describes extracts of Aleppo galls containing ellagic acid in combination with gallic acid and hydrolyzable tannins, and an application in cosmetics as an ultraviolet B protection filter and in a preventive role against the harmful effects of free radicals, which are responsible for skin ageing.

It is further known that type VII collagen, hereafter referred to as collagen VII, is the predominant constituent of the anchoring fibrils associated with the basal membrane joining the epidermis to the dermis. It is synthesized by the keratinocytes of the basal layer of the epidermis and to a lesser extent by the fibroblasts of the dermis, as described by R. Burgeson in the publication entitled "Type VII collagen, anchoring fibrils, and epidermolysis bullosa", J. Invest.

Dermatol. (1993) 101, 252-255. Reference may also be made to the publication by A. Koenig et al. in J. Invest. Dermatol. (1992) 99 808-812. It will be noted in this connection that, according to recent studies, topical applications of retinoic acid increase the number of anchoring fibrils on skin which has undergone actinic ageing (Woodley D.T. et al., J. Amer. Med. Assoc. (1990) 263, 3057-9). Now, retinoic acid, or tretinoin, is recognized as being one of the most effective antiwrinkle agents (L.H. Kligman, Cutis (1988) 41 (6) 419-20; J.J. Leyden et al., J. Am. Acad. Dermatol. (1989) 21 (3Pt 2) 638-44; J.H. Saurat, Horm. Res. (1995) 43 (1-3) 89-92).

According to the publication by Y.Q. Chen, A. Mauviel, J. Ryynanen, S. Sollberg, J. Uitto ("Type VII collagen gene expression by human skin fibroblasts and keratinocytes in culture: Influence of donor age and cytokine responses", J. Invest. Dermatol. (1994) 102, 205-209), certain manifestations of skin ageing, such as increased delicacy of the skin and reduced ability of the epidermis to repair itself, might be attributable to a decrease in the synthesis of collagen VII in elderly subjects. It will be noted that the expression "delicacy of the skin" particularly covers the appearance of blisters at the sub-basal level.

In J. Invest. Dermatol. (1995) 105 844-850, M. Akiyama et al. described that collagen, particularly collagen VII, played an important role at the level of the human hair follicle, especially at the level of the basal membranes of the matrix (peripapillary zone) and at the level of the basal membrane of the bulge (at the top of the bulb). These two zones contain cells of high mitotic potential, particularly keratinocytes which produce the hair shaft.

Finally, it is also known that the dermis-epidermis cohesion is of prime importance for the basal populations of the epidermal keratinocytes to have an optimum metabolism, a good cohesion thus enabling them in particular to assure the formation of a good-quality, elastic and well-formed corneal layer with optimum internal hydration which respects the functionalities of the cellular layers. A good dermis-epidermis cohesion thus participates in the formation and maintenance of skin at metabolic equilibrium, giving it especially a good esthetic appearance.

Within the framework of the present invention, it was surprisingly discovered that ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or polyacylated derivatives afforded a significant increase in the proportion of collagen VII in a medium in which normal human keratinocytes were present.

This finding led to the development of a novel cosmetic, pharmaceutical or especially dermatological composition useful more particularly in all applications where it is desired to increase the proportion of collagen VII, particularly with a view on the one hand to favoring the cohesion between the dermis and the epidermis, and on the other hand, at the level of the hair follicles of the scalp, to contributing towards the restoration or maintenance of the functionality of the cells, particularly the keratinocytes. This property proved particularly useful for the preparation of topical, cosmetic or dermatological compositions.

Such compositions make it possible in particular to favor the cohesion between the dermis and the epidermis in persons whose skin is atonic or loose. They can also be useful in hair care for improving hair condition, promoting the growth of good-quality hair or slowing down or delaying hair loss. They also make it possible to treat pathological conditions accompanied by a deficiency of the dermal-epidermal junction, such as epidermolysis bullosa.

Thus, according to a first feature, the invention relates to the use of ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or poly-acylated derivatives as a cosmetic agent for improving the cohesion between the dermis and the epidermis, said agent preferably being incorporated into a cosmetic composition comprising a cosmetically acceptable vehicle.

Advantageously, the improvement in the cohesion between the dermis and the epidermis is realized by reinforcing the dermal-epidermal junction.

According to a second feature, the present invention also covers the use of ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or polyacylated derivatives as a cosmetic agent for increasing the proportion of collagen VII, said agent preferably being incorporated into a cosmetic composition comprising a cosmetically acceptable vehicle.

Within the framework of the invention, it has in fact been clearly demonstrated that, surprisingly, the action of ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or polyacylated derivatives is to increase the proportion of collagen VII.

Thus the compositions of the invention prove particularly useful in all applications where it is desired to improve the cohesion between the dermis and the epidermis.

Within the framework of the invention, the ellagic acid salts include particularly metal salts, especially those of alkali metals or alkaline earth metals such as sodium and calcium, amine salts such as those of methylglutamine,

diethanolamine, triethanolamine, choline and bis-triethylamine, and amino acid salts, especially those of basic amino acids such as arginine, lysine and ornithine, the metal complexes include particularly those with zinc and copper, and the mono- or polyacylated derivatives comprise particularly saturated or unsaturated acyl groups having from 2 to 22 carbon atoms. These acyl groups preferably correspond to acetic, palmitic, oleic, linoleic, linolenic, arachidonic, stearic, brassidic, erucic, behenic and (all Z)-5,8,11,14,17-eicosapentaenoic acids. The above-mentioned mono- or polyether derivatives are particularly derivatives of alkoxy comprising from 1 to 4 carbon atoms, or condensation derivatives of one or more of the hydroxyl groups of ellagic acid with a sugar or a chain of sugars. In particular, said derivatives are 3-methoxyellagic acid or mono- or polyether derivatives with sugars such as glucose, arabinose, rhamnose and galactose.

The above-mentioned ether or acylated derivatives can be obtained by polyphenol etherification or acylation processes well known to those skilled in the art. Some of them can also be obtained by extraction from plants.

In addition, the ellagic acid, its metal complex salts or its mono- or polyether or mono- or polyacylated derivatives will be particularly intended for toning up the skin, preventing or delaying the appearance of signs of skin ageing, delaying the appearance of wrinkles or reducing their depth, and improving hair condition.

The invention thus relates in particular to antiwrinkle products, products for combating skin ageing, particularly natural skin ageing, and loosening of the skin, or of a hair care lotion such as a lotion for combating hair loss.

Consequently, the invention makes it possible to prepare particularly valuable cosmetic compositions for combating skin ageing, particularly actinic ageing of the skin, i.e. ageing induced by radiation, particularly solar radiation and very particularly ultraviolet solar radiation.

In general terms, the cosmetic compositions of the invention prove particularly useful as skin toning products, particularly for combating loose or atonic skin.

According to a third feature, the invention further relates to the use of ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or polyacylated derivatives for the preparation of a pharmaceutical composition, especially dermatological composition, for treating pathological conditions associated with a deficiency in the cohesion between the dermis and the epidermis, particularly conditions associated with a weakening of the dermal-epidermal

junction, such as epidermolysis bullosa, or for treating manifestations or pathological conditions associated with an insufficiency of collagen VII.

The cosmetic or pharmaceutical compositions, especially dermatological compositions, of the invention will advantageously contain from 0.0001% to 5% by weight, preferably between 0.01 and 1% by weight, of ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or polyacylated derivatives, based on the total weight of the composition.

As a further advantage, the compositions of the invention may comprise at least one substance which favors the synthesis of the constituents of the extracellular matrix of the skin and/or regulates the formation of a good-quality corneal layer.

Examples of such substances which may be mentioned are vitamins, particularly vitamins of groups A and C, and their derivatives such as esters, tocopherols, xanthines, particularly caffeine or theophylline, retinoids, particularly vitamin A acid, extracts of Centella asiatica, asiatic and madecassic acids and their glycosylated derivatives such as asiaticoside or madecassoside, extracts of Siegesbeckia orientalis, extracts of Commiphora mukul and extracts of Eriobotrya japonica, and mineral elements, preferably magnesium, manganese, silicon and zinc, these mineral elements advantageously being used in the form of the chloride in the case of magnesium and manganese, in the form of silanol in the case of silicon and in the form of aspartate in the case of magnesium.

Furthermore, the composition according to the invention can also contain at least one substance selected from the group consisting of aliphatic C_3-C_{12} alpha-hydroxy acids, particularly citric acid, malic acid and lactic acid, amino acids, particularly arginine, citrulline and threonine, ceramides, glycoceramides, phospholipids, slimming agents, forskolin, extracts of Coleus, extracts of Tephrosia, agents for combating stretch marks, particularly extracts of horse-chestnut and escin, agents for protecting or improving the microcirculation, particularly the bioflavonoids of Ginkgo biloba, and sun filters, particularly titanium oxides, acyl methoxycinnamate (Parsol MCX®) and filters of vegetable origin.

In the compositions of the invention which are intended more particularly for hair treatment and care, the ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or polyacylated derivatives will advantageously be associated with at least one other active principle selected from the group consisting of antidandruff agents such as extracts of Arctium lappa, chloroxylenol,

resorcinol or zinc pyrithione, antiseborrhea agents such as a 5α-reductase inhibitor, particularly an extract of Pygeum africanum, and agents for stimulating the blood microcirculation, such as cepharanthine and methyl nicotinate.

The formulations can take a variety of forms. One of the most widely used forms is a topical form suitable for application to the skin tissue. Without implying a limitation, these appropriate topical formulations include emulsions, creams, milks, balms, gels, lotions and medicated make-up compositions.

According to other features, the invention further relates to a method of cosmetic or pharmaceutical treatment, especially dermatological treatment, aimed at increasing the proportion of collagen VII.

The invention further relates in particular to a method of cosmetic treatment for improving the cohesion between the dermis and the epidermis, particularly by reinforcing the dermal-epidermal junction, for toning up the skin, for preventing or delaying the appearance of signs of skin ageing, for delaying the appearance of wrinkles or reducing their depth, and for improving hair condition, characterized in that it consists in delivering a cosmetically effective amount of ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or polyacylated derivatives, optionally contained in a cosmetically acceptable excipient.

Embodiments of this method, in particular, naturally result from the foregoing description relating to the compositions.

Other objects, characteristics and advantages of the invention will become clearly apparent to those skilled in the art from the following explanatory description relating to several Examples, which are given simply by way of illustration and cannot in any way limit the scope of the invention. The Examples form an integral part of the invention. Also, in the Examples below, the percentages are indicated by weight, the temperatures are in degrees Celsius and the pressure is atmospheric pressure, unless indicated otherwise.

EXAMPLES OF THE INVENTION

Example 1

Demonstration of the activity of ellagic acid in increasing the proportion of collagen VII in a culture of normal human keratinocytes

The test below was carried out on ellagic acid available from Extra Synthèse, France, in the form of a powder melting above 360°C.

The tests were carried out blind on normal human keratinocytes.

1 - Test protocol

a) Origin of the keratinocytes:

The cultures of normal human keratinocytes (NHK) are prepared from a surgical sample of healthy skin. In the present study, the tests were carried out on two strains of cells originating from face-lifts performed on a 49-year-old caucasian woman, denoted by NHK 1124, and a 50-year-old caucasian woman, denoted by NHK 1106.

b) Culture conditions:

The keratinocytes are kept in complete serum free medium (denoted by SFMc, GIBCO). The cells were subcultured once or twice from the primary culture (i.e. one pass, denoted by P1, or two passes, denoted by P2) before being used for the test.

c) Treatment conditions:

The cells are inoculated in a 96-well culture plate at a rate of 25,000 NHK per well in SFMc. After incubation for 24 h, which is necessary for good adhesion of the cells, the medium is replaced with SFMc diluted to 2% to limit the proliferation of the keratinocytes during the test. The test concentration of ellagic acid is 0.5 microgram per ml of test medium, which is obtained immediately beforehand from a stock solution containing 0.5 mg of ellagic acid per ml of DMSO. The final concentration of DMSO in the test medium is therefore 0.1% V/V_{final}. This concentration is not toxic to the cells. The control consists of SFMc test medium diluted to 2%, to which 0.1% V/V of DMSO has been added. Six cultures are prepared for the test product and six for the control experiment.

The cells are brought into contact with the treatment medium for 72 h.

The incubation supernatants are removed for assay of the collagen VII. A

protein assay is carried out on the tapetum of cells remaining in the wells (BCA method, SIGMA) for the purpose of relating the amounts of collagen VII to those of cellular proteins.

A plate treated in parallel is used for the XTT viability test with the XTT kit from Boehringer, reference 146 50 15, in order to measure the mitochondrial dehydrogenase activity of the viable cells. No significant drop in viability was detected by this test or by microscopic observation of the cells at the test concentration of 0.5 µg (microgram) per ml.

d) ELISA of the collagen VII:

The protocol for assay of the collagen VII by an ELISA method was adapted from that used to assay collagen I (M. DUMAS, C. CHAUDAGNE, F. BONTE, A. MEYBECK: "In vitro biosynthesis of type I and III collagens by human dermal fibroblasts from donors of increasing age", Mechanisms of Ageing and Development, 73 (1994) 179-187).

The following modifications were made:

- 1st antibody: mouse monoclonal antibody against human type VII collagen, IgG1 isotype (Life Technologies, ref. 12073-011, batch FB2b01).

- 2nd antibody: goat antibody against total mouse IgGs, coupled with alkaline phosphatase (Interchim, ref. 115-056-062, batch 26793).

The alkaline phosphatase activity is disclosed by cleavage of the substrate paranitrophenyl phosphate (PNPP) to paranitrophenol, whose absorbance is measured at 405 nanometers.

e) Expression of the results and statistical interpretation:

The results of the increase in the proportion of collagen VII in the keratinocyte culture are expressed as the activity of the ellagic acid, denoted by A, where A is expressed as a percentage and corresponds to the following formula:

$$A = \left(\frac{RODC_{ea} - RODC_{ks}}{RODC_{ks}}\right) \times 100$$

where:

- The subscript "ea" corresponds to the values associated with a keratinocyte culture prepared in the presence of ellagic acid.

- The subscript "ks" corresponds to the values associated with a keratinocyte culture prepared in the absence of ellagic acid, which is also called a control culture.

- ROD corresponds to the reduced optical density:

$$ROD = (OD - OD_{blank})$$

- OD corresponds to an optical density measured following the treatment of a supernatant.

- OD_{blank} corresponds to the optical density measured on the culture medium.

- RODC corresponds to an ROD corrected so as to correspond to an optical density relating to 100 µg of cellular proteins assayed in the well in question.

The results obtained on the treated cultures (n = 6) and control cultures (n = 6) are compared by the unpaired Student test with a chosen significance level of $p < 0.05$.

The activity of the product according to the invention, namely ellagic acid, on the proportion of collagen VII in the culture medium was thus tested on the two different strains of keratinocytes indicated above, referred to as NHK 1124 (P2) and NHK 1106 (P1).

2) Results - Conclusion

The results are given in Table 1 below on the basis of the mean of the measurements on the different cultures:

TABLE 1

ACTIVITY OF ELLAGIC ACID ON THE PROPORTION OF COLLAGEN VII

Strain of keratinocytes	Ellagic acid concentration (μg/ml)	RODC for 72 h of incubation	p (t test) relative to the control culture	A for 72 h of incubation
NHK 1124P2 (F, 49 years, face-lift)	0	0.773 ± 0.023		
	0.5	1.098 ± 0.100	0.0003	+ 42%
NHK 1106P1 (F, 50 years, face-lift)	0	0.950 ± 0.180		
	0.5	1.563 ± 0.240	0.0007	+ 64%

The results given in Table 1 show a large and significant increase in the proportion of collagen VII present in the culture media due to the presence of the ellagic acid according to the invention at a concentration of 0.5 μg/ml.

As collagen VII is in particular the main constituent of the anchoring fibrils, it is clearly apparent from this test that ellagic acid and its derivatives according to the invention can advantageously be used as agents for reinforcing the dermal-epidermal junction and thereby improving the cohesion between the dermis and the epidermis. Ellagic acid and its derivatives according to the invention can therefore advantageously be used in cosmetic "antiwrinkle", "anti-ageing" and "toning" compositions as well as in dermatological compositions for combating epidermolysis bullosa.

It is further known that collagen VII plays an important role at the level of the human hair follicle, which is why, given the experimental results above, there is great interest in ellagic acid and its derivatives according to the invention for hair care and, in general terms, for improving hair condition.

Example 2 of the invention

Cosmetic toning composition:

- Ellagic acid commercially available from Extra Synthèse, France 0.01 g
- Extract of Centella asiatica 0.1 g
- Perfumed emulsified excipient in the form of an oil-in-water emulsion, and preservative QSP 100 g

This composition combats loosening of the skin and restores its firmness. It can advantageously be used for 3-week courses of treatment by application to the areas of the body to be treated where the skin is loose.

Example 3 of the invention

"Anti-ageing" emulsion

- Acetate of ellagic acid 0.02 g
- Vitamin A palmitate 0.01 g
- Perfumed fluid emulsified excipient QSP 100 g

This emulsion can be used on the areas of the body to be treated, particularly on the face, preferably every evening. It contributes towards delaying the appearance of signs of skin ageing, such as wrinkles or loosening of the skin. After daily treatment for about 6 months, the skin becomes smoother, more supple and firmer. It regains its radiance.

Example 4 of the invention

Cosmetic toning and "anti-ageing" emulsion

This emulsion is prepared from the following 3 phases A, B and C:

Phase A	
- Emulgade SE® (1)	6 g
- Cetyl alcohol	2 g
- BHT	0.02 g
- Isononyl isononanoate	6 g
- Propylparaben	0.02 g
- Coconut glycerides	6 g
- Centella asiatica	0.1 g
Phase B	
- Methylparaben	0.2 g
- Distilled water	67.64 g
Phase C	
- Ellagic acid	0.01 g
- Butylene glycol	12 g
- Vitamin A palmitate	0.01 g

(1) Emulgade SE® is a composition from HENKEL which is a mixture of glyceryl stearate (and) ceteareth-20 (and) ceteareth-10 (and) cetearyl alcohol (and) cetyl palmitate.

Phase C is prepared first by subjecting a mixture of the ellagic acid and the butylene glycol to an ultrasonic treatment for 15 minutes. The vitamin A palmitate is then added.

The fatty phase A and the aqueous phase B are heated together to 85°C. At 85°C, phase B is emulsified with phase A by mechanical agitation. Agitation is maintained while the resulting emulsion is cooled to 45°C, at which temperature agitation is continued for 45 minutes.

Phase C is added to the phase A/phase B emulsion, which is maintained at 45°C, with agitation. This agitation is continued for 5 minutes after phase C has been added.

This emulsion can be used on the areas of the body to be treated, particularly on the face, preferably every evening. It contributes towards delaying the appearance of signs of skin ageing, such as wrinkles, reducing the depth of the latter or combating loosening of the skin. After daily treatment for about six

months, the skin becomes smoother, more supple and firmer.

Example 5 of the invention

Cosmetic toning and "anti-ageing" emulsion

This emulsion is prepared with the following compounds:

- Distilled water	67.53 g
- Butylene glycol	12.00 g
- Emulgade SE®	6.00 g
- Isononyl isononanoate	6.00 g
- Coconut glycerides	6.00 g
- Cetyl alcohol	2.00 g
- Methylparaben	0.20 g
- Centella asiatica	0.10 g
- Vitamin A palmitate	0.10 g
- Sodium salt of ellagic acid	0.03 g
- BHT	0.02 g
- Propylparaben	0.02 g

The composition Emulgade SE® is described in the previous Example.

This emulsion can be used on the areas of the body to be treated, particularly on the face, preferably every evening. It contributes towards delaying the appearance of signs of skin ageing, such as wrinkles, reducing the depth of the latter or combating loosening of the skin. After daily treatment for about six months, the skin becomes smoother, more supple and firmer.

Example 6 of the invention

Dermatological preparation in the form of a gel for the treatment of epidermolysis bullosa

- Zinc complex of ellagic acid	0.01 g
- Butylene glycol	10 g
- Absolute ethanol	20 g
- Distilled water	54.99 g
- Carbomer (Ultrez®-10 gel from GOODRICH) at a concentration of 2%	15 g

This gel can be applied locally, three times a day for at least fifteen days, to the areas to be treated in cases of epidermolysis.

Example 7 of the invention

"Antidandruff" lotion for combating hair loss

A hair lotion is prepared using 0.01 g of zinc complex of ellagic acid, 0.005 g of chloroxylenol and 0.01 g of cepharanthine with a perfumed alcoholic excipient to make up to 100 g.

The lotion is used by application to the scalp, morning and evening, followed by a gentle massage. After 8 to 15 days of treatment, hair loss has been distinctly slowed down and the itching sensation has disappeared. The recommended courses of treatment are for 30 days with intervals of 2 to 4 months, depending on the magnitude of the hair problem to be treated.

Example 8 of the invention

Cosmetic toning and "anti-ageing" emulsion

- Ellagic acid	0.50 g
- Vitamin A palmitate	0.01 g
- Centella asiatica	6.00 g
- Excipient with preservative	QSP 100.00 g

This emulsion can be used on the areas of the body to be treated, particularly on the face, preferably every evening. It contributes towards delaying the appearance of signs of skin ageing, such as wrinkles, reducing the depth of the latter or combating loosening of the skin. After daily treatment for about six months, the skin becomes smoother, more supple and firmer.

CLAIMS

1. Use of ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or polyacylated derivatives as a cosmetic agent for improving the cohesion between the dermis and the epidermis, said agent being incorporated into a cosmetic composition comprising a cosmetically acceptable vehicle.

2. Use of ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or polyacylated derivatives as a cosmetic agent for increasing the proportion of collagen VII, said agent being incorporated into a cosmetic composition comprising a cosmetically acceptable vehicle.

3. Use according to claim 1 or 2, characterized in that said composition is intended for toning up the skin, preventing or delaying the appearance of signs of skin ageing, and delaying the appearance of wrinkles or reducing their depth.

4. Use according to claim 3, characterized in that the skin ageing is actinic ageing due in particular to the action of solar radiation.

5. Use according to claim 2, characterized in that said composition is a hair composition for improving hair condition.

6. Use of ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or polyacylated derivatives for the preparation of a pharmaceutical composition, especially dermatological composition, for treating pathological conditions associated with a deficiency in the cohesion between the dermis and the epidermis, particularly conditions associated with a weakening of the dermal-epidermal junction.

7. Use of ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or polyacylated derivatives for the preparation of a pharmaceutical composition, especially dermatological composition, for treating manifestations or pathological conditions associated with an insufficiency of collagen VII.

8. Use according to claim 6, characterized in that said composition is intended for treating epidermolysis bullosa.

9. Use according to one of claims 1 to 8, characterized in that the ellagic acid salts include metal salts, particularly those of alkali metals or alkaline earth metals such as sodium and calcium, amine salts such as those of methylglutamine, diethanolamine, triethanolamine, choline and bis-triethylamine, and amino acid salts, especially those of basic amino acids such as arginine, lysine and ornithine, the metal complexes of ellagic acid include those with zinc and copper, the mono-

or polyacylated derivatives comprise saturated or unsaturated acyl groups having from 2 to 22 carbon atoms, these acyl groups preferably corresponding to acetic, palmitic, oleic, linoleic, linolenic, arachidonic, stearic, brassidic, erucic, behenic and (all Z)-5,8,11,14,17-eicosapentaenoic acids, and the above-mentioned mono- or polyether derivatives are derivatives of alkoxy comprising from 1 to 4 carbon atoms, or condensation derivatives of one or more of the hydroxyl groups of ellagic acid with a sugar or a chain of sugars, particularly 3-methoxyellagic acid or its mono- or polyether derivatives with sugars such as glucose, arabinose, rhamnose and galactose.

10. Use according to one of claims 1 to 9, characterized in that said composition contains from 0.0001% to 5% by weight, preferably between 0.01% and 1% by weight, of ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or polyacylated derivatives, based on the total weight of the composition.

11. Use according to one of claims 1 to 10, characterized in that said composition also contains at least one substance which favors the synthesis of the constituents of the extracellular matrix of the skin and/or regulates the formation of a good-quality corneal layer.

12. Use according to claim 11, characterized in that said substance is selected from the group consisting of vitamins, particularly vitamins of groups A and C, and their derivatives such as esters, tocopherols, xanthines, particularly caffeine or theophylline, retinoids, particularly vitamin A acid, extracts of Centella asiatica, asiatic and madecassic acids and their glycosylated derivatives such as asiaticoside or madecassoside, extracts of Siegesbeckia orientalis, extracts of Commiphora mukul and extracts of Eriobotrya japonica, and mineral elements.

13. Use according to claim 12, characterized in that the above-mentioned mineral elements are selected from magnesium, manganese, silicon and zinc, these mineral elements advantageously being used in the form of the chloride in the case of magnesium and manganese, in the form of silanol in the case of silicon and in the form of aspartate in the case of magnesium.

14. Use according to one of claims 1 to 13, characterized in that said composition also contains at least one substance selected from the group consisting of aliphatic C_3-C_{12} alpha-hydroxy acids, particularly citric acid, malic acid and lactic acid, amino acids, particularly arginine, citrulline and threonine, ceramides, glycoceramides, phospholipids, slimming agents, particularly forskolin, extracts of

Coleus, extracts of Tephrosia, agents for combating stretch marks, particularly extracts of horse-chestnut and escin, agents for protecting or improving the microcirculation, particularly the bioflavonoids of Ginkgo biloba, and sun filters, particularly titanium oxides, acyl methoxycinnamate and filters of vegetable origin.

15. Use according to one of claims 1 to 14, characterized in that said composition also contains at least one other active principle selected from the group consisting of antidandruff agents such as extracts of Arctium lappa, chloroxylenol, resorcinol or zinc pyrithione, antiseborrhea agents such as a 5α-reductase inhibitor, particularly an extract of Pygeum africanum, and agents for stimulating the blood microcirculation, such as cepharanthine and methyl nicotinate.

16. Method of cosmetic treatment for improving the cohesion between the dermis and the epidermis, particularly by reinforcing the dermal-epidermal junction, for toning up the skin, for preventing or delaying the appearance of signs of skin ageing, for delaying the appearance of wrinkles or reducing their depth, and for improving hair condition, characterized in that it consists in delivering a cosmetically effective amount of ellagic acid, its salts, its metal complexes or its mono- or polyether or mono- or polyacylated derivatives, optionally contained in a composition comprising a cosmetically acceptable excipient, particularly in a form as defined in one of claims 9 to 15.

ABSTRACT

The invention relates to the use of ellagic acid and its derivatives in the field of cosmetics and pharmacy, especially dermatology.

It relates more particularly to all applications where it is desired to reinforce the dermal-epidermal junction or improve hair condition by increasing the proportion of collagen VII in the presence of keratinocytes and/or fibroblasts.

In particular, these applications involve toning up the skin, reducing wrinkles or improving hair condition.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF ELLAGIC ACID AND ITS DERIVATIVES IN COSMETICS AND DERMATOLOGY

the specification of which (check only one item below):

☐ is attached hereto.

☐ was filed as United States application

Serial No. _____

on _____,

and was amended

on _____ (if applicable).

☒ was filed as PCT international application

Number PCT/FR98/02098

on OCTOBER 1st, 1998,

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowlege the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
FRANCE	97 12227	1st OCTOBER 1997	☒ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

Usa Cum #61-

Combined Declaration For Patent Application and Power of Attorney (Continued)
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowlege the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U S APPLICATIONS		STATUS *(Check one)*		
U S APPLICATION NUMBER	U S FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U S					
PCT APPLICATION NO	PCT FILING DATE	U S SERIAL NUMBERS ASSIGNED *(if any)*			

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(List name and registration number)*

Donald L. DENNISON, Reg.N°19920; Burton SCHEINER, Reg.N°24018
William H. MESEROLE, Reg.N°20833; Ira J. SCHULTZ, Reg.N°28666
David POLLACK, Reg. N° 20478; Jeffrey S. SMITH, Reg.N°39377

Send Correspondence to:
DENNISON, MESEROLE, POLLACK & SCHEINER
1745 Jefferson Davis Highway, Suite 612
ARLINGTON VIRGINIA 22202

Direct Telephone Calls to: *(name and telephone number)*
(703) 412 1155

201 FULL NAME OF INVENTOR 1-00	FAMILY NAME: BONTE	FIRST GIVEN NAME: Frédéric	SECOND GIVEN NAME:	
RESIDENCE & CITIZENSHIP	CITY: 45100 ORLEANS FRX	STATE OR FOREIGN COUNTRY: FRANCE	COUNTRY OF CITIZENSHIP: FRANCE	
POST OFFICE ADDRESS	POST OFFICE ADDRESS: 54 rue Tudelle	CITY: 45100 ORLEANS	STATE & ZIP CODE/COUNTRY: FRANCE	
202 FULL NAME OF INVENTOR 2-00	FAMILY NAME: SAUNOIS	FIRST GIVEN NAME: Alex	SECOND GIVEN NAME:	
RESIDENCE & CITIZENSHIP	CITY: 45100 ORLEANS FRX	STATE OR FOREIGN COUNTRY: FRANCE	COUNTRY OF CITIZENSHIP: FRANCE	
POST OFFICE ADDRESS	POST OFFICE ADDRESS: 2, rue Daniel Mayer	CITY: 45100 ORLEANS	STATE & ZIP CODE/COUNTRY: FRANCE	
203 FULL NAME OF INVENTOR	FAMILY NAME:	FIRST GIVEN NAME:	SECOND GIVEN NAME:	
RESIDENCE & CITIZENSHIP	CITY:	STATE OR FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:	
POST OFFICE ADDRESS	POST OFFICE ADDRESS:	CITY:	STATE & ZIP CODE/COUNTRY:	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
Frédéric Bonté	Alex Saunois	
DATE: 17 MARCH 2000	DATE: 17 MARCH 2000	DATE: